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Mitochondria Initiate and Regulate Sarcopenia

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Abstract

We present the hypothesis that an accumulation of dysfunctional mitochondria initiates a signaling cascade leading to motor neuron and muscle fiber death and culminating in sarcopenia. Interactions between neural and muscle cells that contain dysfunctional mitochondria exacerbate sarcopenia. Preventing sarcopenia will require identifying mitochondrial sources of dysfunction that are reversible.

Graphical abstract

Summary for TOC: Sarcopenia is characterized by fiber atrophy and loss of fibers. Mitochondria health determine death signaling leading to localized protein loss and if unchecked, widespread loss of muscle fibers.

Keywords

Muscle wasting; autophagy; apoptosis; aging; sarcopenia; ubiquitin proteasome; lysosome

Introduction

Sarcopenia, is associated with increased levels of apoptosis (47) and reduced capabilities for muscle regeneration (41) leading to muscle wasting. For this reason, many studies including our own have focused on the muscle specific signaling that contribute to muscle wasting in sarcopenia. However, sarcopenia in aged humans and rodents is also associated with motor neuronal death (96, 139), which causes impaired innervation (48, 106), and a ~27% reduction in the motor unit pool. In aging, a loss of innervation induces profound muscle atrophy (5, 106, 129). Some denervated fibers become innervated by axons from surviving

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motor neurons (42, 45), whereas other fibers remain denervated and contribute to functional losses in sarcopenia (42).

We postulate that the tight relationship between the loss of motor neurons and muscle cells in aging is explained by a common underlying mechanism that initiates deterioration in these cells. It is interesting that a loss of mitochondria function with aging is a mechanism that is shared by both muscle cells (18, 63) and motor neurons (123). Our current perspective and hypothesis is that mitochondrial deterioration in muscles and motor neurons is the primary initiator of sarcopenia (**Figure 1**). We have identified some of the data that support this perspective, and the areas that are speculative and require additional work to test this hypothesis.

Mitochondrial regulation of sarcopenia - Hypothesis

Aging increases mitochondrial stress that sensitizes the opening of the mitochondria transition permeability pore (mPTP). A loss of mitophagy-proteasome-induced mitochondrial clearance in muscle and motor neuron cells promotes accumulation of poorly functioning mitochondria that have increased mPTP opening. Leakage of the mitochondrial contents to the cell cytosol initiates death (apoptosis) signaling in muscle cells and motor neurons, which contributes to nuclear DNA fragmentation and if not repaired, nuclear apoptosis. Removal of nuclei in muscle cells and motor neurons leads to fiber and motor neuron death and loss of innervation to the muscle cells. Cross talk between muscles and motor neurons that contain dysfunctional mitochondria exacerbates sarcopenia. Thus, mitochondria are key initiators and regulators of sarcopenia **(Figure 1).**

Sources for mitochondrial damage in aging muscles and motor neurons—Our working hypothesis is that sarcopenia is initiated by an aging-associated insult to mitochondria in muscle cells and motor neurons. Mitochondrial stress in aging can originate from greater levels of oxidants, DNA damage, or denervation (31, 133).

Reactive oxygen species (ROS) induced damage—Aging increases ROS production (22), and lowers antioxidant enzymes levels in muscle and neuron cells (58, 59, 121). ROS production might be secondary to denervation that occurs in muscles from old animals or humans (48, 55, 133). The accumulation of ROS has the potential to damage cellular mitochondria (reviewed in (15)). The importance of antioxidants in sarcopenia is highlighted by observations that both neural and muscle losses of the cytosolic antioxidant CuZn-superoxide dismutase (CuZnSOD) recapitulated sarcopenic muscle loss in a mouse model (125). It is noteworthy that the absence of CuZnSOD in either neural or muscle cells did not manifest full sarcopenic muscle loss (125). However, this observation highlights the need to consider cross talk between these two tissues in aging. Whatever the initial source(s) of ROS production, it is clear that accumulation of excessive ROS contributes to damaged and dysfunctional mitochondria in muscle and neural cells.

Mitochondrial DNA damage and aging in motor neurons and muscle cells—Mitochondrial DNA (mtDNA) deletions or DNA mutations contribute to mitochondrial dysfunction and aging-related muscle fiber loss and atrophy (50, 90). In neurons, DNA

damage precedes neuronal apoptosis (85), whereas forced repair of DNA damage rescues neurons from elimination by apoptosis (86). Indeed, increased mtDNA mutations have been found in fiber regions that contain oxidative damage (2, 90). Furthermore, aging-induced mtDNA deletions are closely associated with a loss of mitochondrial function in motor neurons (123), neuronal malfunction in diseases like Parkinson's disease (115), and muscle loss with aging (50, 91). While elevated ROS production is not solely the result of mtDNA deletions or mtDNA mutations (141), it is clear that this mechanism contributes to mitochondrial ROS production in aging muscles and neurons (26, 86, 91).

Mitochondria permeability transition pore sensitization with aging – mitochondrial dysfunction

Stress-induced damage to mitochondrial membranes (40, 108, 144, 147) contributes to sensitization of the mitochondrial permeability transition pore (mPTP) (44). The mPTP is a large conductance pore in the inner mitochondrial membrane, which is predominantly closed under non-stressed conditions. Opening of the mPTP can be induced by ROS, increased concentrations of Ca^{2+}, or mitochondrial depolarization. mPTP opening is further exacerbated by an imbalance of Ca^{2+} homeostasis that likely results from leaky ryanodine receptors in aged skeletal muscle (10). Excessive Ca^{2+} loading leads to mitochondrial swelling, and rupture of the outer mitochondrial membrane.

Opening the mPTP induces a further loss of mitochondrial membrane potential, and releases the mitochondrial contents to the cytosol to initiate apoptotic signaling (24, 77, 89). Apoptosis signaling has been reported in muscle and neuronal cells of aged rodents (4, 7, 26, 34, 47, 77, 88, 130), and humans (44, 145). Aging-associated muscle denervation may also contribute to increased mPTP opening, that in turn induces apoptosis and muscle loss (76, 133).

Similar to skeletal muscle cells, ROS damage to mitochondria in neurons from aged animals contributes to mPTP opening (53). This occurs through p66Shc which generates H_2O_2 that in turn, reacts with cytochrome c and induces oxidation of the mPTP and mitochondrial swelling (126). This mechanism is similar to neural degenerative diseases where induction of ROS (80, 113) contributes to motor neuron death (116). Thus, mitochondrial susceptibility to mPTP opening is a common point which triggers downstream cell destruction in both neuron and muscle cells.

Insufficient mitophagy allows unhealthy mitochondria to persist in aging muscles and neurons

Damaged mitochondria normally undergo fission then they are finally removed by mitophagy. However, mitophagy is attenuated with aging in skeletal muscle and motor neurons (40, 63, 70, 127). AMP-activated protein kinase (AMPK) and Sirtuin 1 (SIRT1) trigger the destruction of dysfunctional fragmented mitochondria through FoxO3-dependent autophagy (mitophagy) (94, 118). Mitofusin 2 (Mfn2) has an important role regulating mitochondrial fusion, but it also acts a receptor for Pink1 and Parkin-targeted mitophagy

(27). Recent data by Sebastián and colleagues (127) show that Mfn2 declines in muscle with aging and loss of Mfn2 produces an aging-like phenotype, including age-associated mitochondrial dysfunction, higher ROS accumulation and muscle fiber atrophy. Mfn2 has also been implicated in the loss of mitophagy in motor neurons. For example, a reduced inhibition of the E3 ligase Omi/HtrA2 in neuronal mitochondria contributes to a decrease in Mfn2 leading to attenuated mitophagy (29). Thus, an aging associated deficiency of Mfn2 may be the bridge between impaired mitophagy and an accumulation of dysfunctional mitochondria in muscle and neurons during sarcopenia. However, it should be pointed out that other evidence does not support a decrease in Mfn2 or a decrease in the Mfn2 to Drp1 ratio that would be expected if Mfn2 were suppressed in muscles of aged mice (75).

Defective mitophagy underlies the progression of motor neuron death in Amyotrophic lateral sclerosis (ALS) (38). In contrast, lithium-induced induction of mitophagy (38, 101) and mitochondrial biogenesis (101) improves mitochondrial morphology in motor neurons of a G93A SOD-1 mouse model of ALS. Other autophagy proteins, including Pink152, which is the cleavage product of the mitochondrial autophagy protein Pink1, has been implicated in the attenuation of mitophagy in motor neurons. Pink152 can exit the mitochondria in neuron cells and cleave Parkin, which then suppresses its translocation to the mitochondria to attenuate mitophagy (36).

Contrary data suggest that mitophagy may be increased in aging muscles as evidenced by greater migration of Parkin and p62 to the mitochondria (103). Nevertheless, an accumulation of lipofuscin granules suggests a failure of the lysosome to remove dysfunctional mitochondrial in aging even when Parkin has translocated to the mitochondria (103). Indeed, lipofuscin deposits have been reported previously in many tissues including muscles and neurons of aged rodents or other mammals (138). Further work is needed to determine if lysosomal dysfunction (136), loss of Mfn2, or some other protein involved in mitochondrial dynamics regulates mitophagy in sarcopenia.

Local apoptotic signaling in aging muscles and motor neurons becomes more wide spread to result in cell death

Our hypothetical model to explain the loss of single muscle fibers in sarcopenia is shown in **Figure 2**. This model assumes that local mitochondrial damage (potentially via ROS, high calcium loads, mtDNA damage etc.) causes increased mPTP opening, which triggers the contents of the mitochondria to leak to the cytosol. This initiates the intrinsic apoptotic signaling pathway leading to DNA fragmentation and nuclear apoptosis in a localized region of the fiber. An aging-suppression of autophagy activators like Sirtuin 1 (SIRT1) and Mfn2 or other proteins involved in mitophagy, prevents removal of dysfunctional mitochondria via mitophagy and proteasome digestion.

The regional accumulation of damaged mitochondria could extend to other regions within the fiber via their connecting reticular network. As dysfunctional mitochondria accumulate, the region of the fiber that is engulfed by death signaling is expanded. We predict that eventually the entire fiber would be eliminated, presumably by involving the proteasome.

Genes of necrosis may also contribute to the overall cellular removal as sarcopenia progresses (26).

Cardiolipin is an important mitochondria-specific phospholipid, which is concentrated between inner and outer mitochondrial membranes, and redistribution of cardiolipin leads to a localized oligomerization of proapoptotic proteins (83). A local apoptotic cascade could occur via restricted remodeling and redistribution of cardiolipin adjacent to dysfunctional mitochondria. Furthermore, interaction of cardiolipin with the structural protein vimentin (104) could provide a localized cell-signaling site for targeted apoptotic disassembly and removal via anti-vimentin/CL complex antibodies, as has been observed in several pathologies involving apoptosis (104).

Our model for a localized apoptotic and proteolytic signaling cascade that expands to neighboring regions of a muscle fiber (**Figure 2**) has strong support from the work of Aiken and co-workers (26, 49, 50). For example, Cheema *et al.* (26) observed a localized aging-induced loss of the mitochondrial enzymes succinate dehydrogenase and cytochrome *c* oxidase. Interestingly, the same fiber region that had mitochondrial disruption was both atrophic and had high levels of the apoptotic protein caspase-3. In contrast, fiber atrophy and apoptotic signaling did not occur in other regions of the same muscle fibers that were located further away from the dysfunctional mitochondrial (26). If the degenerative processes were not initiated locally but rather from a more general or systemic source, we would expect uniform muscle fiber wasting across its length, but this is not the case. Nevertheless, we predict that the progression of sarcopenia involves a gradual shift from targeted proteins in regions close to dysfunctional mitochondria to a strategy of non-targeted cellular destruction by activating the proteasome pathway when the apoptotic signaling expands to a wider fiber area.

We recognize that mitochondria are represented as distinct organelles in this simplistic model of localized signaling shown in **Figure 2**. However, mitochondria can range from small individual organelles, to rather extensive and connected reticular systems (57). In our model, mitophagy would be expected to target the regional area near dysfunctional mitochondria via the Pink1/Parkin and the LC3-II/autophagy receptor system for lysosomal removal. Although speculative, it is possible that elimination of a section of dysfunctional mitochondria could occur without disruption to the entire network of mitochondria along its reticulum. This could occur by activating fission signaling to wall off a healthy region of the mitochondrial reticulum from a region of dysfunctional mitochondria. Indeed, increased mitochondrial fission dynamics have been reported after muscle denervation (57) and in aging (55, 62). On the other hand, insufficient mitophagy in muscles from very old hosts could permit mitochondrial dysfunction in one area to affect other regions along the same mitochondrial reticulum and therefore affect a wider region of the cell.

We speculate that similar to our model in skeletal muscle fibers, motor neurons in aging hosts have increased mPTP opening, leading to apoptotic signaling, but dysfunctional mitochondrial are not removed because mitophagy is suppressed in aging. The apoptotic disassembly of motor neurons could begin regionally near dysfunctional mitochondria and spread to a wider area, resulting in motor neuronal death. Our speculation is supported from

data that show that in aging-associated neural diseases, there is a loss of mitochondrial function leading to increased mPTP sensitivity, and attenuated mitophagy that contributes to apoptosis (32, 68, 86, 99, 111). Nevertheless, we do not have data to support a process of aging associated localized motor neuron disassembly outside of neural degenerative disease. Additional work is needed to determine if localized loss of mitochondrial function contributes to a regional concentration of apoptotic signaling in motor neurons in the same way that it might occur in skeletal muscle cells with aging.

Altered mitochondrial dynamics with aging

Abnormal mitochondrial dynamics may negatively affect mitochondrial health. For example, both the mRNA level and the protein abundance of important fusion and fission proteins have been reported to be lower in old as compared to young adult skeletal muscle (55), and this would suggest that the potential for mitochondria to respond to changing environments might be reduced as compared to mitochondria from young hosts. Indeed, this appears to be the case, because electron microscopy and biochemical analyses have shown small, more fragmented mitochondria in muscles from old as compared to young adult hosts (56, 57), although very large mitochondria have also been noted in muscles from old animals (75). Consistent with the fragmented mitochondrial phenotype in muscles from old hosts, there is evidence to suggest that muscles of aged rodents and humans have a greater overall rate of fission vs. fusion (55, 62) and lower levels of the fusion protein Opa1 (62) as compared with younger muscles. Fragmented mitochondria tend to have a lower respiratory capacity, and a greater production of ROS, which increases the susceptibility of mitochondria to release its contents and activate the intrinsic caspase apoptotic pathway. Thus, it is not surprising that aging and disuse, which both have excessively fragmented mitochondria, are accompanied by muscle loss (57). It is interesting that a knockout of Mfn 1/2 in skeletal muscle, which prevented mitochondrial fusion, increased the accumulation of mtDNA defects and resulted in muscle atrophy (31). Together, these observations support for the idea that muscle mitochondria are important regulators of muscle size. However, to provide a balanced perspective it is important to point out that other studies have found higher fusion profiles in muscles of humans (14), and prematurely aged mice (63), and larger mitochondria in muscles of old mice (75). It is interesting that studies that have reported a higher fusion index in muscles from old rodents as indicated by ratios of Mfn1/Mfn2 (63) or Mfn2/Drp1 (75) did not find changes in the protein contents of Mfn1, Mfn2, Opa1 or Drp1. Thus, even when higher fusion indexes are recorded there still may be more fragmented mitochondria in aged muscles

The impact of age-associated changes in the mitochondrial dynamics of motor neurons and their potential role in sarcopenia have not been studied. However, dysfunction of mitochondrial dynamics has been reported as an early event in Amyotrophic lateral sclerosis (61) which is a common motor neuron disease. Furthermore, increased mitochondrial fragmentation has been found to precede glutamate-induced death of motor neurons (143). Thus, similar to mitochondrial dynamic changes that have been proposed in muscle with aging, motor neuron dysfunction and death may converge upon mitochondria, and mitochondrial dynamics may play an important role in regulation of neuronal function that contributes to accelerated sarcopenia.

FOXO proteins and the ubiquitin proteasome system (UPS) in muscle atrophy and sarcopenia

An acceleration of protein turnover with a net loss of protein is downstream of dysfunctional mitochondria but this represents a major contributor to sarcopenia. AMPK activation (118) and the Forkhead box class O (FOXO) transcription factor family regulates the ubiquitin proteasome system (UPS), and the autophagy-lysosome system. FOXO proteins also regulate the UPS, which is a tightly regulated system responsible for normal intracellular protein turnover and elimination of misfolded and dysfunctional proteins (72, 74). FOXOs control the mammalian target of rapamycin complex 1 (MTORC1) signaling, which is associated with muscle hypertrophy (43) and inhibition of mitophagy in skeletal muscle (23). FOXO regulation also occurs by MTORC1-mediated phosphorylation of ULK1 at Ser757 and the subsequent activation of the ULK1-ATG13- RP6KB/ribosomal protein p70S6 kinase (RB1CC1) in the UPS (23). Inhibition of MTORC1 in muscles of tuberous sclerosis complex (TSC) knockout mice, mimic many features of aging. This includes a loss of muscle mass and strength and attenuated mitophagy (23). However, protein turnover is tightly controlled because MTORC1 is upregulated in denervation-induced muscle atrophy (135). Interestingly, inhibition of MTORC1 reduced muscle atrophy via suppression of E3 ligases, Muscle RING Finger 1 (MuRF1) and MAFbx/atrogin in response to denervation (135).

FOXO control of the UPS is important in the final steps of degradation of proteins in sarcopenia. FOXOs activate lysosomal cathepsins and cytosolic protease calpains which progresses towards ATP-dependent UPS activation via FOXO3a associated MuRF-1 and MAFbx regulation [reviewed in (66, 117)]. Thus, FOXO mediated autophagy via the UPS may be an important regulator of muscle mass in aging. In future studies it will be important to determine if failure to regulate FOXO control of MTORC1 or perhaps failure of other proteins that are in the pathways of anabolism might contribute to increased degradation of muscle proteins in aging.

Conflicting data highlight the complexity of understanding the importance of the UPS and atrogenes in sarcopenia. For example, ubiquitin (17), 26S proteasome, poly-ubiquitinated proteins (3), MuRF-1 and MAFbx expression were all reported to be elevated in hindlimb muscles of sarcopenic rats as compared to young adult animals (3, 30). Furthermore, ubiquitin was found to be greater in quadriceps muscles of older (70-79 yrs old) human subjects as compared to young adults (20-29 yrs old) (17). In contrast, MuRF-1 and MAFbx expression were reported to be lower in muscles of old rats than young adult rats (35) and not changed with aging in vastus lateralis of humans (145). The discrepancy between these studies might be due to variability introduced by a low number of subjects or animals in each study, and perhaps by some differences in the age and sex of the subjects that were studied. It is also possible that activity, nutritional history, health and smoking habits etc. will have affected MuRF-1 and MAFbx regulation in these studies. Thus, additional studies are warranted to understand the importance of the UPS in sarcopenia and the role of mitochondria in regulating the UPS more fully.

UPS disruption increases dysfunctional mitochondria in muscle and neural cells

Aging associated neural diseases like Parkinson's and Alzheimer's disease, are associated with high ROS levels in neural cells. Reduced mitophagy associated Pink1- and Parkin-regulated ubiquitination of the outer mitochondrial membrane of damaged mitochondria in aged neurons (79, 99, 140) contribute to a greater accumulation of ROS (81). High ROS can damage more mitochondria in muscle and neurons (81) and potentially elevate ROS levels even higher. It is therefore likely that proteasome dysfunction contributes to the higher potential for ROS generation in muscles and neuron cells of older individuals or animals.

An association between the UPS and mitochondria occur through a splice variant of the master mitochondrial regulator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). PGC-1α2, PGC-1α3, and PGC-1α4, have been shown to stimulate protein synthesis and attenuate UPS activity in cultured myotubes and mouse skeletal muscle (87, 119). Furthermore, PGC-1α reduces muscle protein degradation by the UPS via blocking nuclear factor κB (NF-κB) and FoxO3 activity (16, 124).

Cross talk between mitochondrial regulators of autophagy and the UPS

There is considerable communication between the UPS, mitochondrial regulators and governors of autophagy. For example, silent mating type information regulation 2 homolog 1 (SIRT1) appears to be part of a pathway that regulates mitophagy. This pathway also involves AMPK, a master energy sensor (20). AMPK increases NAD^+ levels, which activates NAD^+-dependent SIRT1. Activated SIRT1 deacetylates and activates PCG-1α which promotes mitochondria synthesis, assembly, growth and mitochondrial antioxidant production (54). Deacetylation of FOXO1 and FOXO3a by SIRT1 (19, 20) mediates autophagic signaling in muscle cells, and aging attenuates SIRT1, which reduces autophagy (134). Furthermore, overexpression of SIRT1 reduces muscle wasting and innervation-induced muscle atrophy by deacetylation and inhibiting FOXO1a and FOXO3 thereby inhibiting induction of MuRF-1 and MAFbx. Future studies should establish the relative importance of cross talk between PGC-1α, FOXO, SIRT1 and the UPS in aging muscles and motor neurons and establish how this affects sarcopenia.

Communication between mitochondrial induced death signaling in muscle and motor neuron cells accelerate cell death in aging

Cross talk between muscle and motor neurons are important to both tissues. This has been known for several decades, because when toxins or other compounds are injected into muscles, the compounds undergo retrograde transport to the neuromuscular junction (105), deposit in motor neurons (11), and sometimes contributes to motor neuronal dysfunction (reviewed in (33, 39). This communication is also seen when spinal cord injury or denervation induces large-scale muscle wasting (57, 76, 107, 129, 131, 137), and denervation is a condition often seen as part of sarcopenia. High levels of apoptotic signaling (1, 129) and altered autophagy signaling (102, 103) with elevated UPS activity (137) occurs in muscles after spinal cord injury or denervation. Thus, we would expect that altered neuronal signaling is due at least in part to high ROS production and mitochondrial dysfunction in the muscle cells, and conversely, that neural dysfunction will be communicated to muscle cells (57, 100).

The health of muscle cells also affects motor neuron health. For example, increased muscle activity in male G93A SOD1 deficient mice contributes to greater motor impairment and motor neuron accelerated death (82). This implies that a feedback loop exists that conveys information about muscle activity and the condition of the muscle to the motor neuron. Further evidence of a muscle to motor neuron feedback pathway is supported from data showing increases in mitochondrial succinate dehydrogenase (SDH) activity in motor neurons following functional overload of the plantaris hindlimb muscle in cats (25). Furthermore, the presynaptic motor endplate of the neuromuscular junction is critical for providing retrograde transport to the motor neuron (98).

Observations from aging rats suggests that mitochondria in the axon terminals of the neuromuscular junction undergo swelling, in part from calcium overload. The resulting dysfunction of mitochondrial metabolism and dynamics contributes to elevations in cytosolic cytochrome c and caspase-3 (39). Furthermore, inhibition of synaptic loss reduces apoptosis of motor neurons in a mouse model of motor neuron disease (37). Together, these observations confirm that the same mitochondrial-induced initiation of apoptosis signaling that occurs in skeletal muscle also occurs in neuromuscular junctions with aging. We speculate that in aging, motor neurons receive feedback from deteriorating muscles and neuromuscular junctions and this communication in turn feeds to a loop of accelerated mitochondrial-induced degenerative changes in motor neurons. Although we cannot rule out the possibility that mitochondrial-induced apoptotic signaling and cell death may occur independently in muscle and motor neuron cells in aging, we have illustrated potential general feedback routes between muscle and motor neuron comparts that may affect the other tissue type, and if this occurs, we would expect sarcopenia to be accelerated (**Figure 1**). Clearly, additional studies are need to test for the presence of these potential communication loops in aging.

Perspectives for Future Progress and the need for Future Studies

Our hypotheses is based on some speculation and therefore additional work is needed to test these hypotheses. Even if the mitochondrial centered hypothesis for sarcopenia is true, there are unknown factors that would be important to study in order that the information can make a practical impact on sarcopenia. A few of these questions are: As mitochondria damage may occur in several different ways (e.g., ubiquination, acetylation, succinylation, ROS damage to inner membrane, mtDNA damage, etc.), which of these (or other pathways) are the most important to sensitize mPTP opening to trigger apoptosis? What is the best strategy to combat mitochondrial dysfunction in aging? If exercise is considered to be a tool for reducing mitochondrial dysfunction, how would exercise target dysfunctional mitochondria? Is it necessary for muscle and neuron cells to improve mitochondria number or just remove dysfunctional mitochondria to slow or prevent sarcopenia? These questions are explored below, but the lack of clear information emphasizes the need for additional studies to provide these answers.

What is the most important source of mitochondrial damage that triggers apoptosis and cell death?

We have focused on ROS damage to the inner mitochondrial membrane (15, 21, 22, 79) and mtDNA damage (22, 26, 50, 63, 73) as two important ways that might impair mitochondrial function in aging muscles and motor neurons. However, mitochondria damage and modifications may also occur by posttranslational modifications such as ubiquitination (67, 99, 140, 148), acetylation (9, 21, 28), succinylation (114, 150), and phosphorylation (51, 73, 79). Other potential sources of mitochondrial damage include excessive calcium loading (9, 28). Likely some damage is repairable, whereas other damage contributes to irreparable mPTP opening leading to nuclear apoptosis and cell death. It is important to identify which of these (or other pathways) provide potential reversible mitochondrial damage and which cause irreversible damage that promotes apoptosis.

Potential strategies using exercise and nutrition to reduce sarcopenia should focus on mitochondrial health

Exercise interventions and nutritional manipulations have produced some successes for reducing although not fully eliminating sarcopenia. A logical place to begin the search for ways by which exercise and nutritional approaches might better attenuate sarcopenia is by targeting these strategies to maximize mitochondria health. This includes identifying the mitochondrial modifications that are reversible by exercise and nutritional interventions in aging. For example, mitochondrial acetylation is reversible at least under some circumstances including exercise (97). Proteins like SIRT1 and SIRT3 may be important regulators of deacetylation in mitochondria (46, 97, 132). SIRT1 is important for deacetylation of mitochondrial-interacting targets like PGC-1α, FOXO3, p53 and NF-kB (Reviewed in (13, 110) and has been implicated in improving function and life span in aging (95). Furthermore, SIRT1 deacetylation of Mfn2 may be important for regulating mitophagy and removing dysfunctional mitochondria (132). In addition, evidence from non-muscle and non-neuronal cells suggests that mPTP-mediated pore opening and apoptosis can be inhibited by deacetylation of mitochondria by SIRT3 (46).

Exercise training and nutrition could be used as an intervention to increase SIRT1 and SIRT3 activity with the goal of increasing mitophagy and mitochondrial biogenesis pathways in muscle and neuronal cells. However, aging is associated with high cell levels of ROS and ROS accumulation is an inductor for mPTP opening. ROS accumulation could increase with exercise, and this may be why exercise has only been partially successful in reducing sarcopenia. We postulate that nutritional regulation of oxidants should be considered to minimize the additional ROS burden (58, 59, 120-122) when initiating exercise training in the elderly to minimize mPTP opening. Future studies could test if nutritional antioxidants would minimize excessive ROS accumulation, oxidant damage and mPTP opening in muscles and neurons when elderly persons begin an exercise program. If this were the case, we would predict that antioxidant supplements should be slowly reduced after some duration of training adaption has past, to permit cellular increases in SIRT1/SIRT3 and antioxidant defenses for the elderly subjects without risking excessive ROS damage.

How might exercise target dysfunctional mitochondria by mitophagy?

Studies in rodents have shown an increased abundance of autophagy proteins including Drp1 and Bcl-2 and 19 kDa interacting protein-3 (Bnip3) after exercise (60, 65, 71, 78). Bnip3 functions as a mitophagy receptor to recruit selected autophagosomes for elimination. Exercise-induced Pink1 activation of Drp1 (112) could also target dysfunctional mitochondria for mitophagy. This idea is supported by recent data from Mejias-Pena et al. (92) who found an increase in the protein abundance of autophagy proteins Beclin-1, Atg12, Atg16, and the LC3II/I ratio in blood mononuclear cells of elderly subjects after 8 weeks of aerobic exercise. Furthermore, 8 weeks of aerobic exercise has been reported to increase autophagy proteins Beclin-1, ATG7, and MuRF-1 in muscles of old mice (70). Indeed, it has been proposed that autophagy signals are necessary to achieve aerobic improvements in skeletal muscle (78). Thus, autophagy proteins may be important for an exercise-mediated slowing of sarcopenia. If the same processes occur in humans as is the case in rodents and non-human mammals (64), exercise, or nutritional intervention such as caloric restriction would also be expected to increase mitophagy removal of dysfunctional mitochondrial, so the mitochondria that remain are proportionally healthier (64).

Although clearly speculative, we postulate that in response to exercise or nutritional interventions, mitochondria that are the most dysfunctional would provide the greatest magnitude of apoptotic signaling and be more likely to attract autophagy linker proteins (e.g., p62) for elimination by mitophagy. Future studies are needed to identify the precise signatures of local death signaling around individual dysfunctional mitochondria and to determine which autophagy receptors are reduced by exercise or nutritional interventions and to examine if activated LC3-II is attenuated or eliminated once dysfunctional mitochondria are removed. This will take technology that is able to identify dysfunctional from healthy mitochondria and sample the milieu adjacent to each mitochondria.

Although speculative, exercise or nutritional modifications might target dysfunctional mitochondria for elimination is via an autophagy pathway called chaperone-mediated autophagy (CMA). CMA involves the binding of constitutive heat shock 70 to selected proteins, which are targeted to the lysosomal membrane where they interact with membrane receptor lysosomal-associated membrane protein 2A (LAMP2A). Aging causes degradation and availability of LAMP2A in the lysosomal membranes (69), which reduces the effectiveness of CMA. Future studies should evaluate the role of LAMP2A and determine if exercise or nutritional interventions increase CMA and target dysfunctional mitochondrial for mitophagy in muscles and motor neurons of old animals or humans.

Another potential way that exercise could selectively target dysfunctional mitochondria is through elevation of Parkin or the degradation of PARK7/DJ-1 (142). PARK7 is an antioxidant protein that limits mitochondrial damage in response to oxidative stress (12) and it regulates skeletal muscle contractile protein synthesis and hypertrophy (149). Overexpression of PARK7 reduces mitochondrial dysfunction under oxidative stress (142) which shows a direct link between autophagy and mitochondrial function. Future studies should identify if exercise or nutritional intervention (e.g., antioxidants, caloric restriction) improves PARK7 expression in muscles and motor neurons of old hosts and if the change in PARK7 directly mediates improvements in mitochondrial function of skeletal muscle.

Parkin and Pink1 are attractive candidates for targeting dysfunctional mitochondria, which we speculate would occur in response to exercise. This is because accumulation of Pink1 at the outer mitochondrial membrane provides a precise mechanism to identify dysfunctional mitochondria from healthy ones. Pink1 promotes Parkin recruitment to activate mitophagy and UPS signaling. However, overexpression of PGC-1α was reported to attenuate Pink1 levels in response to remobilization of muscle (67). As we would expect exercise to increase mitochondrial biogenesis through the PGC-1α axis, it is not known if Pink1 plays an important role in an exercise-mediated increase in mitophagy of muscle cells and motor neurons of aged humans or rodents.

The potential role for mitochondrial biogenesis to reduce sarcopenia

In addition to increasing mitophagy, exercise and nutritional interventions might be expected to increase mitochondrial biogenesis and therefore replace the dysfunctional mitochondria that are removed by mitophagy. Both endurance and resistance exercise have been associated with elevated mitochondrial biogenesis (93, 109). Relative mitochondrial activity corresponds with fractional protein synthesis rates, because many proteins complete their translation at mitochondria (84). There is an assumption that endurance and strength training by older adults induces mitochondrial biogenesis, but given the propensity for mtDNA damage and high ROS levels in aging, this remains uncertain. If newly synthesized mitochondria were generated in exercised muscles and motor neurons from aged hosts, but the new mitochondrial were unhealthy (e.g., incompletely folded proteins), the mitophagy signals (from exercise or nutritional interventions) would need to be even higher to remove these newly formed but dysfunctional mitochondria. Clearly, additional work is needed before we fully understand if exercise or nutritional interventions synthesize completely functional and healthy mitochondria in aged hosts, or if the basal environment of oxidative stress etc. results in a new population of unhealthy mitochondria that must also be targeted for mitophagic removal in the elderly.

We know that exercise downregulates apoptosis and upregulates mitophagy (4, 52, 128, 146). Nevertheless, future studies should explore the mechanisms by which exercise activates mitophagic, and attenuates apoptotic, and necrotic signaling pathways in muscle cells and motor neurons of older individuals (4, 47). We recognize that increased apoptosis and reduced mitophagy have not been identified as an aging-related condition in every study, but in our view, there is sufficient data to suggest that this is probably an underlying process for most cells in aging. Nevertheless, some of the mitochondrial mediated pathways leading to motor neuron death in aging have not received much attention and should be the investigation of future work.

Future experiments should also identify novel proteins and protein functions that better define the communication of dysfunctional signaling between motor neurons and muscle cells in aging. Modern genetic approaches, including RNA-seq and proteome pathway analysis, will likely be required. It will also be important to find out if it is possible to reverse the process responsible for regional disassembly in the absence of mitochondrial biogenesis, and then to focus on molecular events and targets in muscle and motor neurons that are upstream of this point. In the quest to attenuate sarcopenia, it will also be important

to understand the limit for mitochondrial health to impact satellite cell function for repairing and replacing sections of fibers or whole fibers, as satellite cells are affected adversely by aging, mitochondrial damage and death signaling (4, 6, 7, 144).

Conclusions

Mitochondrial-regulated apoptosis provides a strong signaling network that contributes to sarcopenia (8). We have taken the perspective that both neural and muscle components contribute to muscle wasting but mitochondrial health is central to initiating and perpetuating the signal for sarcopenia. We argue that mitochondrial dysfunction leads to increased mPTP opening and initiates apoptotic signaling in muscle cells and motor neurons. In aging, this is not corrected because mitophagy is inhibited. Proteasome activation leads to removal of cellular contents close to the site of dysfunctional mitochondria, and this cellular dismantling expands proportionally to the accumulation of dysfunctional mitochondria. Although aging induces wide spread systemic mitochondrial dysfunction, perhaps as a result of high ROS or accumulation of mtDNA damage, we have considered that retrograde and anterograde communication likely exists between dying muscle and motor neurons, which may accelerate death in both compartments.

Additional studies are needed to establish if exercise and nutrition can be used to effectively improve mitochondria health and reduce sarcopenia in aging populations. In our view, targeting dysfunctional mitochondria and increasing healthy mitochondria in motor neurons and muscle fibers provide the best strategy for reducing sarcopenia.

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Key Points

- Aging-induced mitochondrial insult in muscle and neurons (e.g., oxidative stress, DNA damage, posttranslational modifications) results in mitochondrial permeability transition pore opening.
- Mitophagy signaling normally removes dysfunctional mitochondria, but this process is impaired in aging muscle cells and motor neurons.
- Release of the contents from dysfunctional mitochondria to the cytosol initiates local apoptotic signaling, that if left unchecked activates nuclear fragmentation, cell death and proteasome activation for cell removal.
- Cross talk between dysfunctional muscle and motor neuron cells exacerbates the sarcopenic loss of muscle mass and function.
- To prevent sarcopenia, future studies should identify strategies that reverse mitochondrial modifications to prevent opening of the mitochondrial permeability pore and increase mitophagy in muscle and neuronal cells.

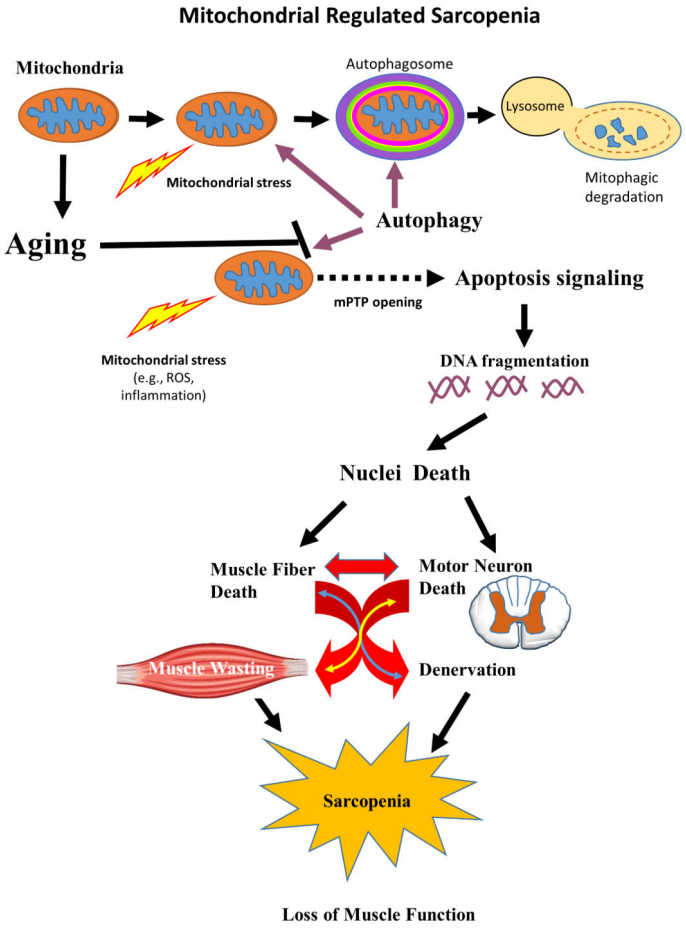

Figure 1. Mitochondrial Regulated Sarcopenia

Induction of mitochondrial stress (lightning bolt) can result in dysfunctional mitochondria. Damaged mitochondria are engulfed in an autophagosome membrane and removed by mitophagy signaling in healthy young muscle and motor neurons. However, aging is associated with increased ROS and other mitochondrial stresses, which enhance mPTP opening. Release of the mitochondrial contents to the cell cytosol induces an apoptotic cascade ending with DNA fragmentation and removal of nuclei. Sufficient nuclear death in muscle cells will result in the death and removal of the entire muscle cell. Similarly, motor neuron death occurs when apoptosis removal of the alpha motor neuron nucleus occurs. The interdependence of muscle cells and motor neurons suggests a potential feedback loop (anterograde and retrograde) communication between the muscle and the motor neuronal compartments, which exacerbates death in both compartments. Death in these cell compartments leads to loss of muscle mass and function in aging. Thus, dysfunctional mitochondria provide the signal to initiate sarcopenia.

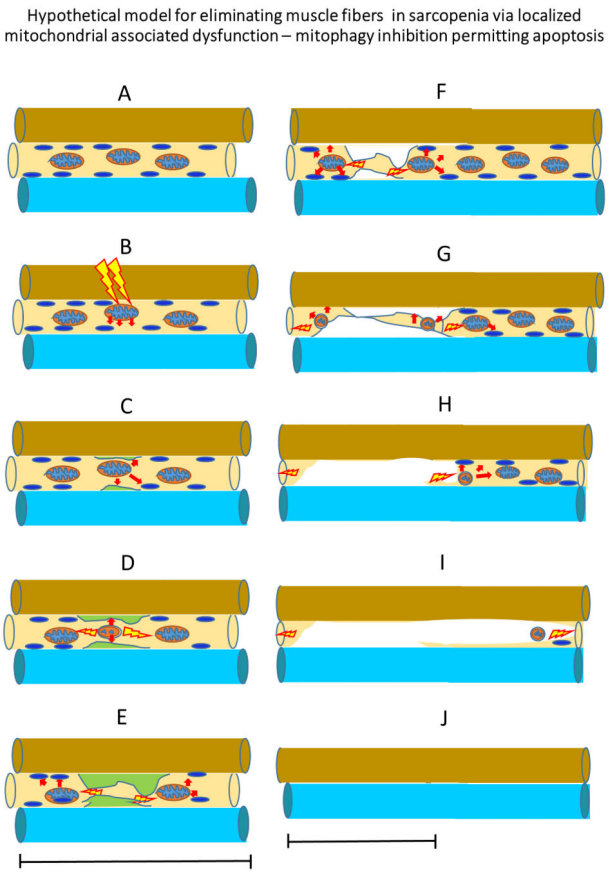

Figure 2. Hypothetical model for eliminating muscle fibers in sarcopenia via localized mitochondrial associated dysfunction – mitophagy and apoptosis

A. In healthy muscle, activation of mitophagy eliminates dysfunctional nuclei so that they cannot continue death signaling. **B.** Dysfunctional mitochondria that leak their contents to the cytosol will occur in muscle that has received a significant mitochondrial stress (e.g., ROS, inflammatory mediators etc.). **C-D.** This initiates the apoptotic signaling cascades. **E-F.** If the dysfunctional mitochondria are not eliminated, apoptotic death signaling may be activated to eliminate myonuclei and this may concurrently or independently result in wide-spread activation of autophagy and the ubiquitin ligase pathway and also, trigger the necrosis signaling pathway to remove muscle proteins, mitochondria and nuclei within the domain of the initial dysfunctional mitochondria (**G-H**). **I-J.** The extent of dysfunctional mitochondrial will extend along the mitochondrial reticular network and affect the function of other mitochondria near the dysfunctional mitochondrial. The wider accumulation of dysfunctional mitochondria will perpetuate signaling for apoptosis, which will remove nuclei from a larger area. The greater nuclear loss will be followed by elevated proteasome signaling to eliminate contractile and non-contractile tissue in the fiber segment that is associated with dysfunctional mitochondria and apoptotic signaling. This cellular removal will result in eventual elimination of the portion of the fiber in the area of the dysfunctional mitochondrial and potentially the entire fiber. We further hypothesize that the initiation of the disassembly and removal of the fiber could be blocked if the dysfunctional mitochondria which initiate the process, are removed or the damage to mitochondria reversed (e.g., via

exercise and nutritional interventions) and if irreparable damaged mitochondria are replaced by healthy mitochondria.